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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,248	04/09/2001	Billy F McCutchen	BB1208PCT	4178

7590 11/21/2003

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EXAMINER	
GOLDBERG, JEANINE ANNE	
ART UNIT	PAPER NUMBER
1634	

DATE MAILED: 11/21/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,248	MCCUTCHEN ET AL.	
	Examiner	Art Unit	
	Jeanine A Goldberg	1634	

-- The MAILING DATE of this communication appears on the c ver sh et with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21 and 23-33* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21 and 23-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This action is in response to the papers filed September 11, 2003. Currently, claims 21, 23-33 are pending.

2. All arguments have been thoroughly reviewed but are deemed non-persuasive for the reasons which follow. This action is made FINAL.

3. Any objections and rejections not reiterated below are hereby withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

7. Claims 21-31 and newly amended 32-33 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific asserted utility or a well established utility.

The claims are drawn to an isolated polynucleotide consisting of a nucleotide sequence encoding a polypeptide having sodium channel agonist activity wherein the polypeptide has an amino acid sequence of SEQ ID NO: 9.

The specification teaches Zilbergberg determined that single amino acid residues are important for receptor binding and for biological activity of scorpion Na channel toxins (page 1, lines 19-20). The specification provides specific examples which illustrate single amino acid changes cause a substantial decrease in biological activity

and others change in structures. The specification also teaches that the role of Na-channels have been less clearly studied (page 1, lines 28-29). The specification briefly describes two toxins which have different chemical and pharmacological properties. The specification concludes that "thus, other toxins derived from scorpion venom will also have different chemical and pharmacological properties" (page 3, lines 5-10). The specification asserts that SEQ ID NO: 9 is a scorpion neurotoxin I polypeptide (page 3, lines 15-16). The specification compares the neurotoxin I of the instant invention (SEQ ID NO: 9) with the sequence of neurotoxin I from Buthus occitanus tunetanus (SE QID NO: 10) to illustrate the conserved cysteine residues (Figure 2). The specification vaguely alludes to toxin activity assays being confirmed using bioassay, LCMS or antibodies (page 16, lines 5-12). The specification asserts that the presence of toxin activity in the recombinant viruses will be monitored in vivo; compared to wild type; and analyzed using larvae to monitor behavioral changes and mortality (page 16, lines 5-12).

The sequence search illustrates that SEQ ID NO: 9 is 79.3% identical with an alpha insect toxin precursor from Leiurus quinquestriatus. Similarly, SEQ ID NO: 9 is also 75.7% identical with an anti-mammals neurotoxin Bmk9 precursor. The sequence search does not make it clear whether SEQ ID NO: 9 is either an insect or mammalian toxin.

The art teaches that scorpion venoms contain a variety of polypeptide toxins that specifically block or alter gating properties on ion channels (Moskowitz et al. Eur. J. Biochem. Vol. 254, pages 44-49, 1998). Within these toxins exist small and large

polypeptides; mammalian toxins and insect-selective toxins; inset-selective toxins can either be depressant toxins or excitatory toxins (page 44). Moskowitz provides a comparison between similarity between various classes of toxins (page 47). Sautiere et al. (Toxicon, Vol. 36, No. 8, pages 1141-1154, 1998) also provides various classifications between the different toxins.

The post filing date establishes the existence of at least three pharmacological groups of "long-chain" Na channel toxins characterized from the Chinese scorpion Buthus martensii Karsch (BmK) (Zhu et al. Toxicon, Vol. 38, pages 1653-1661, 2000). There three groups each have different pharmacological characteristics. The first group includes alpha-toxins which affect mammals and/or insects through slowing the sodium channel inactivation, such as BmK1, BmK2, BmK3 etc (page 1654). The third group includes depressants insect selective toxins, which induce progressive flaccid paralysis of insects, such as BmKIT2, BmKIT3 and BmKIT4. The fourth group contains the excitatory insect-selective toxins which cause rapid contractive paralysis of insects upon injection such as BmKIT1 (page 1654). It is clear that each of these "toxins" have different properties, different effects and affect different organisms. Zhu discusses placing 9 novel homologues into various groups based upon various differences in single amino acid residues (page 1659).

Neither the art nor the specification teach a specific and substantial utility for the claimed invention. First, the specification nor the art teaches a specific utility to the claimed nucleic acid. The general utility of the nucleic acid as a toxin is not specific since the art teaches that scorpion toxins are classified into several categories based

upon their size, toxicity to certain animals or insects and have different biological and pharmacological characteristics such as whether the toxins are depressant in nature or excitatory. The specification does not teach whether SEQ ID NO: 9 has any particular toxin activity. The specification has assigned SEQ ID NO: 9 as a toxin based upon homology to known toxins. While it is likely that SEQ ID NO: 9 is a toxin it is unpredictable whether SEQ ID NO: 9 is a toxin to mammals and/or insects and whether the toxin acts in an excitatory or depressant manner. The specification has provided no guidance as to the particular function, specificity or biological activities of SEQ ID NO: 9. Therefore, there is no specific utility for the claimed nucleic acid. Moreover, the nucleic acid lacks a substantial utility because the asserted utility as a toxin requires carrying out further research to identify or reasonably confirm a "real world" context of use.

Moreover, the specification fails to provide a clear definition of "having toxin activity." The dictionary provides that toxin is defined as poison produced by living organism (see askoxford.com). Moreover, poison has been defined as substance that when absorbed by living organism kills or injures it. Therefore, it is unclear how one may determine the level of toxin activity required for the claims and how the skilled artisan may determine whether a particular sequence has toxin activity.

With respect to newly added Claims 32 and 33, the claims are drawn to nucleic acids encoding 1-19 and 20-84 of SEQ ID NO: 9 respectively. The specification teaches that amino acids 1-19 contain a signal sequence and amino acids 20-84 contain a mature protein. It is unclear what the signal sequence and the mature protein may be separately used for, as discussed above.

Response to Arguments

The response traverses the rejection. The response asserts that according to Zilberberg "in alpha neurotoxins that are more efficient against insects this stretch reads LysAsnTyrAsnCys, while in the ones that are more efficient against mammals this stretch reads AspAspValAsnCys." Thus, the response asserts that KNYNC is insect efficient and DDVNC is mammal efficient. This argument has been reviewed but is not convincing because the instant amino acid sequence of SEQ ID NO: 9 has a stretch which reads GluAsnTyrAsnCys (ENYNC). The response filed September 11, 2003 asserts that SEQ ID NO: 9 should be more efficient against insects than mammals. Upon review of Figure 2 which illustrates an alignment of SEQ ID NO: 9, the amino acids appear to be QNYNC. There appears to be a difference between the arguments and the Figure with respect to the identity of the first amino acid in the "five amino acid" region. Clarification is required.

However, there is no indication in the specification that at the time of filing that the assumption of a insect efficient toxin was preferred. MPEP 716.01(c) makes clear that "The arguments of counsel cannot take the place of evidence in the record. In re Schulze , 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965). Examples of attorney statements which are not evidence and which must be supported by an appropriate affidavit or declaration include statements regarding unexpected results, commercial success, solution of a long - felt need, inoperability of the prior art, invention before the date of the reference, and allegations that the author(s) of the prior art derived the disclosed subject matter from the applicant." Here, the statements regarding the utility

of the invention must be supported by evidence, not argument. However, the instant specification does not appear to support this assertion.

Additionally, while the SEQ ID NO: 9 may have 4/5 amino acids in common with a partial sequence asserted to be indicative of the insect toxin, this does not indicate that the instant sequence is an insect toxin. The specification has provided no analysis, aside from sequence alignments, in the form of actual toxin activity for SEQ ID NO: 9. There is no indication in the specification that a partial stretch of 5 amino acids would be indicative of an insect toxin. The prior art, namely Zilberberg specifically teaches the importance of position 8 as affecting the affinity for the receptor site (page 14811, col. 2). In fact, Zilberberg teaches that a "severe effect was obtained when the charge at position 8 was inverted by replacing lysine with asparate (K8D). The apparent affinity for the receptor site decreased 1611-fold" (page 14811, col. 2). Zilberberg further teaches that the variant may have changes in the secondary structure. Therefore, the change from Lys in an "insect toxin" to a Glu in the instant SEQ ID NO: 9 would likely affect the toxin in a severe manner since both Asp and Glu are negatively charged R groups. Zilberberg also analyzes the Tyr at position 10, but the position does not appear to have as significant effect as position 8. Zilberberg teaches about the structures of the five-residue turns and states that the bonds between Asp and Lys are different.

In the event that applicant's remarks were intended to recite Gln rather than Glu for the first of the five residues, the differences between the positive charged lysine and

glutamine which is uncharged and polar would require a similar analysis for unpredictability and undue experimentation.

Zilberberg teaches that KNYNC is present in a AaHII and DDVNC is present in LqhalphalahalT, however, Zilberberg does not appear to teach that each of these five-residues are indicative of insect or mammalian toxins. Further, the instant SEQ ID NO: 9 is neither of these five-residue patterns. Thus, the skilled artisan would be required to perform additional research and experimentation to determine the function, specificity or properties and uses for the instant SEQ ID NO: 9.

Thus for the reasons above and those already of record, the rejection is maintained.

Claim Rejections - 35 USC § 112- Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 21-31 and newly amended 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988). *Wands* states at page 1404,

> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are drawn to an isolated polynucleotide consisting of a nucleotide sequence encoding a polypeptide having sodium channel agonist activity wherein the polypeptide has an amino acid sequence of SEQ ID NO: 9.

The specification teaches Zilbergberg determined that single amino acid residues are important for receptor binding and for biological activity of scorpion Na channel toxins (page 1, lines 19-20). The specification provides specific examples which illustrate single amino acid changes cause a substantial decrease in biological activity and others change in structures. The specification also teaches that the role of Na-channels have been less clearly studied (page 1, lines 28-29). The specification briefly describes two toxins which have different chemical and pharmacological properties. The specification concludes that "thus, other toxins derived from scorpion venom will also have different chemical and pharmacological properties" (page 3, lines 5-10). The specification asserts that SEQ ID NO: 9 is a scorpion neurotoxin I polypeptide (page 3, lines 15-16). The specification compares the neurotoxin I of the instant invention (SEQ ID NO: 9) with the sequence of neurotoxin I from Buthus occitanus tunetanus (SE QID NO: 10) to illustrate the conserved cysteine residues (Figure 2). The specification vaguely alludes to toxin activity assays being confirmed using bioassay, LCMS or antibodies (page 16, lines 5-12). The specification asserts that the presence of toxin

activity in the recombinant viruses will be monitored in vivo; compared to wild type; and analyzed using larvae to monitor behavioral changes and mortality (page 16, lines 5-12).

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The post filing date establishes the existence of at least three pharmacological groups of "long-chain" Na channel toxins characterized from the Chinese scorpion Buthus martensii Karsch (BmK) (Zhu et al. Toxicon, Vol. 38, pages 1653-1661, 2000). There three groups each have different pharmacological characteristics. The first group includes alpha-toxins which affect mammals and/or insects through slowing the sodium channel inactivation, such as BmK1, BmK2, BmK3 etc (page 1654). The third group

includes depressants insect selective toxins, which induce progressive flaccid paralysis of insects, such as BmKIT2, BmKIT3 and BmKIT4. The fourth group contains the excitatory insect-selective toxins which cause rapid contractive paralysis of insects upon injection such as BmKIT1 (page 1654). It is clear that each of these "toxins" have different properties, different effects and affect different organisms. Zhu discusses placing 9 novel homologues into various groups based upon various differences in single amino acid residues (page 1659).

Neither the art nor the specification teach the skilled artisan how to use the claimed invention. The art teaches that scorpion toxins are classified into several categories based upon their size, toxicity to certain animals or insects and have different biological and pharmacological characteristics such as whether the toxins are depressant in nature or excitatory. The specification does not teach whether SEQ ID NO: 9 has any particular toxin activity. The specification has assigned SEQ ID NO: 9 as a toxin based upon homology to known toxins. While it is likely that SEQ ID NO: 9 is a toxin it is unpredictable whether SEQ ID NO: 9 is a toxin to mammals and/or insects and whether the toxin acts in an excitatory or depressant manner. The specification has provided no guidance as to the particular function, specificity or biological activities of SEQ ID NO: 9. Therefore, prior to using the invention, the skilled artisan would be required to perform additional undue experimentation to determine the properties of SEQ ID NO: 9 to be able to use SEQ ID NO: 9 in a meaningful way.

Moreover, the specification fails to provide a clear definition of "having toxin activity." The dictionary provides that toxin is defined as poison produced by living

organism (see askoxford.com). Moreover, poison has been defined as substance that when absorbed by living organism kills or injures it. Therefore, it is unclear how one may determine the level of toxin activity required for the claims and how the skilled artisan may determine whether a particular sequence has toxin activity.

With respect to newly added Claims 32 and 33, the claims are drawn to nucleic acids encoding 1-19 and 20-84 of SEQ ID NO: 9 respectively. The specification teaches that amino acids 1-19 contain a signal sequence and amino acids 20-84 contain a mature protein. It is unclear how the skilled artisan would use the signal sequence and the mature protein, as discussed above.

Therefore weighing all evidence provided in the specification and in the art, the skilled artisan would be unable to practice the claimed invention as a whole without further undue and unpredictable experimentation.

Response to Arguments

The response traverses the rejection. The applicant argues the 112/1st and the 101 rejections together. The arguments have been reviewed but are not convincing for the reasons provided above in the 101 rejection. Thus for the reasons above and those already of record, the rejection is maintained.

Conclusion

5. No claims allowable.

6. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner Jeanine Goldberg whose telephone number is (703) 306-5817. The examiner can normally be reached Monday-Friday from 8:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Jones, can be reached on (703) 308-1152. The fax number for this Group is (703) 305- 3014.

Any inquiry of a general nature should be directed to the Group receptionist whose telephone number is (703) 308-0196.

J. Goldberg

Jeanine Goldberg
November 18, 2003

Jehanne Sitton
Jehanne Sitton
Primary Examiner
Nov. 18, 2003